DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group 1, claims 1-11, 21 and 53, in the reply filed on March 26, 2008 is acknowledged. Claims 23-52 are withdrawn from further prosecution. In addition, Applicant has elected SEQ ID NOS: 7 and 8 and the mutation 258+2T>C with traverse. The traversal is on the grounds that there is no burden searching the invention groups or primer sequences since the claims cover overlapping subject matter. This is not found persuasive because burden is not a criterion that determines whether a national stage application filed under 35 U.S.C. 371 is restricted properly. The claims were restricted into Groups I-IX based on the lack of the same or corresponding special technical features, since many of the product claims were found to be anticipated by the prior art. With regard to the primer sequences, each primer sequence is unique and amplifies different SBDS gene sequences and therefore they also lack the same or corresponding special technical feature.

The requirement is still deemed proper and is therefore made FINAL.

Non-compliance to Correction of Sequence Listing

2. In addition, the timely submission filed on March 26, 2008 is not fully responsive to the prior Office action because the request to correct the Sequence Listing was not met in the original restriction requirement mailed December 26, 2007. Since the submission appears to be a bona fide attempt to provide a complete reply to the prior Office action, applicant is given a shortened statutory period of ONE MONTH or THIRTY DAYS from the mailing date of this Action, whichever is longer, to submit a

complete reply. This shortened statutory period supersedes the time period set in the prior Office action. This time period may be extended pursuant to 37 CFR 1.136(a).

Election of SEQ ID NOS: 7 and 8 is acknowledged. However, a search of SEQ ID NOS: 7 and 8 cannot be performed because the SEQ ID NOS in the Sequence Listing do not match the SEQ ID NOS presented in the claims or the specification. For example, SEQ ID NO: 7 in claim 7 matches the sequence of SEQ ID NO: 8 of the Sequence Listing, while SEQ ID NO: 8 in claim 7 matches the sequence of SEQ ID NO: 9 of the Sequence Listing, and thus it is not clear which sequences are intended to represent primers E and F for primer pair (b). In addition, the Sequence Listing is incomplete, as only sequences up to and including SEQ ID NO: 13 appear in the listing, while the claims and the specification contain 34 SEQ ID NOS. An accurate Sequence Listing that matches the SEQ ID NOS of the claims is required to render a meaningful search of the claims.

A copy of this non-compliance letter is also included separately on the record.

Drawings

3. The drawings are objected to under 37 CFR 1.83(a) because they fail to show several features in color as described in the specification, particularly the legends for Figures 1 and 2. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Alternatively, the Figure legends may

be amended, if possible, to accurately describe the drawings in their present form. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

It is noted that color photographs and color drawings are not accepted unless a petition filed under 37 CFR 1.84(a)(2) is granted. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings and black and white photographs have been satisfied. See 37 CFR 1.84(b)(2).

In addition, drawings 2, 4 and 6 are objected to since nucleotide and/or peptide sequences appear in the drawings, but neither the drawings nor the Figure legends identify the sequences using SEQ ID NOS. Correction is required to include SEQ ID NOS in at least in either the drawings or legends.

Claim Objections

4. Claim 1 is objected to because of the following informalities: The term "Schwachman" is spelled differently in the claim compared to the term used in the application title or the specification (Shwachman). Appropriate correction is required. In addition, the acronym SBDS, unlike SDS, is not defined in the claims. Although it is defined in the specification, it is recommended that a definition be provided the first time it appears in the claims, since this is not a commonly-used term in the art.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 6 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not clear what nucleotide sequence the mutations listed in the claims are based upon. The numbering of the mutations does not appear to match the positions in SEQ ID NO: 1 representing the SBDS gene. For example, position 24 of SEQ ID NO:1

is a T nucleotide, while the first mutation in the list is 24C>A. The elected mutation, 258+2T>C also does not appear to occur at position 258 of SEQ ID NO:1 since this position lists an A nucleotide. An explanation of the source of the numbering system of these claims is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-11, 21 and 53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for diagnosing SDS based on some SBDS mutations, does not reasonably provide enablement for diagnosing SDS based on all SBDS mutations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. As discussed below, there are only a limited set of SBDS mutations disclosed in the specification that are significant with respect to predicting whether a subject is suffering from SDS. These include the mutations 183_184TA>CT, 183_184TA>CT + 258+2T>C and 258+2T>C for which the claims are enabled.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-11, 21 and 53 are broadly drawn to methods for determining whether a subject is suffering from Shwachman-Diamond Syndrome (SDS) or is an SDS carrier based on the presence or absence of mutations in the Shwachman-Bodian-Diamond Syndrome (SBDS) gene. However, as will be further discussed, there is only a limited number of mutations disclosed in the specification and supported in the literature that provide enablement for the methods as claimed. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Working Examples

The specification has three working examples on pages 30-33. Example 1 is relevant to the elected claims, describing sequence analysis of the SBDS gene from several SDS-patients. Example 1 of the specification presents evidence that three SBDS mutations listed in Table 1 are significant with respect to predicting whether a

subject is suffering from SDS. These include 183_184TA>CT, 183_184TA>CT + 258+2T>C and 258+2T>C, which occurred in 50%, 5.1% and 4.4%, respectively, of patients in an initial study. These mutations have also been linked with SDS in more recent studies, as discussed below. Therefore, based on the disclosure in Example 1 of the specification as well as the supporting recent literature, the claims are enabled for only these three mutations.

Guidance in the Specification

The specification provides little evidence that the disclosed methods would lead to a successful method for determining whether a subject is suffering from Shwachman-Diamond Syndrome (SDS) or is an SDS carrier. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses that there is a reasonably strong correlation between three mutations found in the SBDS gene and the occurrence of the disease in patients. A number of other mutations are identified in Example 1 and Table 1 as being detected in samples from SDS patients. However, there is no support that these mutations would be useful in a panel of mutations for determining whether a subject is suffering from Shwachman-Diamond Syndrome (SDS) or is an SDS carrier. Furthermore, the specification has not provided definitive primers that can be used for amplification and detection of SBDS mutations since the primers described in the specification do not match those of the sequence listing, and therefore even the skilled artisan would be unable to use the methods of the invention.

The unpredictability of the art and the state of the prior art

There is a great unpredictability in the field of SDS research and the gene associated with this disorder, SBDS. Until 2003, there was no known gene associated

with SDS. Prior to this, a number of studies suggested the disease was linked to various genetic loci on a number of different chromosomes. Finally, the genetic locus for SDS was narrowed to the centromeric region of chromosome 7 in 2001 (Goobie et al., Am. J. Hum. Genet. (2001) 68:1048-1054). Then in 2003 it was shown that mutations in the uncharacterized gene, SBDS, were linked to the disease (Boocock et al., Nature Genet. (2003) 33:97-101; the author list of this reference includes the current inventors), including a number of mutations included in Table 1 and claims 6 and 53 of the instant invention. As were presented in Example 1 and Table 1 of the disclosure, the only mutations that occur with high frequency among the total mutant SBDS alleles are 183_184TA>CT, 183_184TA>CT + 258+2T>C and 258+2T>C, which occurred in 26%, 2.5% and 46%, respectively, of total alleles (this data was presented as a percentage of mutant alleles rather than a percentage of patients). These three mutations were determined to arise through gene conversion due to recombination between SBDS and its pseudogene, and together account for 74% of the total mutant alleles (p. 99, column 1, lines 29-39). A number of other mutant alleles that are not gene conversion mutations occur at well less than 1% of the total mutant alleles. It is noted that about half of these non-gene conversion mutations listed in Table 1 and claims 6 and 53 were also reported by Boocock (see Boocock, Table 1), while Boocock reports an additional mutation, 635T>C, not present in the instant invention.

Since the landmark study of Boocock that definitively linked the SBDS gene to SDS, a number of more recent studies support the initial findings that the gene conversion mutations discovered by Boocock and shown in Table 1 of the specification

are the most significant mutations relevant to determining whether a subject is suffering from Shwachman-Diamond Syndrome (SDS) or is an SDS carrier. In a recent review of SBDS gene mutations detected in SDS patients, most of the gene conversion mutations known to date include one or more of the same three mutations originally reported by Boocock, though sometimes in combination with additional mutations (Costa et al., Blood Cells, Molecules and Diseases (2008) 40:183-184, see Table 1). Several additional novel non-gene conversion mutations have been added to the list originally reported by Boocock.

An earlier studied noted the frequent occurrence of the known gene conversion mutations (such as 183_184TA>CT + 258+2T>C) as well as novel mutations associated with SDS (including 652C>T + 258+2T>C), but also reported several patients with SDS phenotypes but with no SBDS mutations detected (Woloszynek et al. Blood (2004) 104:3588-3590, see Table 1). Thus, while most SBDS mutations were harbored in patients with phenotypically-defined SDS, consistent with the study of Boocock that first linked such mutations with SDS in 2003, the fact that not all SDS patients have SBDS mutations suggests that SDS is a genetically heterogeneous disorder (Woloszynek et al. Blood (2004) 104:3588-3590). Thus, assays that rely on detecting only the known gene-conversion and non-gene conversion mutations may not diagnose all patients that are suffering from Shwachman-Diamond Syndrome (SDS) or are SDS carriers.

Furthermore, another study revealed that SBDS mutations may result in diseases phenotypically distinct from SDS. Samples from two patients revealed known mutations linked to SDS, yet the patients did not display the typical skeletal phenotype of SDS, but

rather severe forms of neonatal spondylometaphysial dysplasia (SMD) (Nishimura et al. J. Med. Genet. (2007) 44:e73, pp. 1-5). One such patient had the recurrent gene conversion mutation 183TA>CT and a novel missense mutation, 79T>C, while a second patient has two recurrent gene conversion mutations, 183TA>CT and 258+2T>C (see Abstract). Several other SMD patients were found to have no SBDS mutations. Thus, while findings of the recurrent SBDS gene conversion mutations appear to be highly linked to SDS, clearly not all such mutations result in SDS, suggesting that SBDS mutations may give rise to variable phenotypes or that unknown mutations are also involved (Nishimura, p. 4, column 2, lines 5-20).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is a significant number of parameters which would have to be studied to apply this method to determining whether a subject is suffering from SDS or is an SDS carrier, even based on the known mutations of the SBDS gene. Since studies suggest that SDS may be a genetically heterogeneous disorder, further experimentation would be required to search for other genes that may be associated with development of SDS. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where mutations in the SBDS often, but not always, indicate that a subject is suffering from SDS or is an SDS carrier, while some SBDS mutations may result in non-SDS disorders, the factor of unpredictability weighs heavily in favor of undue experimentation. Thus, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in determining whether a subject is suffering from SDS or is an SDS carrier, particularly in light of the limited set of SBDS mutations in Table 1 of the specification and claims 6 and 53 that are significantly associated with SDS. Furthermore, the specification has not provided definitive primers that can be used for amplification and detection of the SBDS mutations listed in Table 1 of the specification and claims 6 and 53. Thus, given the broad claims in an art whose nature is identified as unpredictable, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Conclusion

9. Claims 1-11, 21 and 53 are rejected. No claims are allowable.

Correspondence

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David C Thomas/
Examiner, Art Unit 1637

/Teresa E Strzelecka/

Primary Examiner, Art Unit 1637

June 12, 2008